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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

10/796,280

03/10/2004

Michele Cargill

CL001510

9662

25748

7590

07/07/2006

CELERA GENOMICS

ATTN: WAYNE MONTGOMERY, VICE PRES, INTEL PROPERTY

45 WEST GUDE DRIVE

C2-4#20

ROCKVILLE, MD 20850

EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/796,280

Applicant(s)

CARGILL ET AL.

Examiner

Jeanine A. Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 13 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 7-20,23 and 24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,21 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/05</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. This action is in response to the papers filed April 13, 2006. Currently, claims 1-24 are pending. Claims 7-20, 23-24 have been withdrawn as drawn to non-elected subject matter.

### ***Election/Restrictions***

2. Applicant's election with traverse of Group I, Claims 1-6, 21-22 in the paper filed April 13, 2006 is acknowledged.

The response asserts 10 nucleotide sequence should be examined together based upon MPEP Section 803.04. This argument has been thoroughly reviewed but not deemed persuasive because the MPEP provides for up to 10 which encompasses

1. Each of the instant SNPs are patentably distinct and require an undue burden to search and consider together. The resources required to search 10 sequences has dramatically increased since the 1996 OG notice. The volume of data within the databases has grown exponentially. It is no longer reasonable for a search of 10 sequences to be performed in a single application. Moreover, the instant search does not rely solely on the computer resources, but requires a search for SNPs within a gene. Many genes have more than one name and the number of polymorphisms within the gene must be individually searched for novelty. An article which teaches polymorphisms within a gene does not necessarily use the same numbering system, or the same nomenclature. Moreover, many SNPs within Tables are not easily searchable and require burden to analyze the contents of tables within an article which have not

been indexed in the database. Therefore, a search for multiples SNPs in multiple genes is an undue burden on the office.

Claims 7-20, 23-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed April 13, 2006.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 7-20, 23-24 are drawn to an invention nonelected with traverse in the paper filed April 13, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Priority***

3. This application claims priority to provisional applications 60/453,050 filed March 10, 2003 and 60/466437, filed April 30, 2003.

***Drawings***

4. The drawings are acceptable.

***Specification***

5. The title and abstract of the invention is not descriptive of the elected invention. A new title and abstract are required that is clearly indicative of the invention to which the claims are directed.

***Claim Rejections - 35 USC § 112-Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6, 21-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to any single nucleotide polymorphism in SEQ ID NO: 19350. SEQ ID NO: 19,350 is 200 base pairs in length. The specification teaches a single polymorphism at position 101.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2b 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed”. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that “An adequate written description of a DNA...’ required a precise definition, such as by structure, formula, chemical name, or physical properties’, not a mere wish or plan for obtaining the claimed chemical invention”.

With respect to claims which encompass polymorphisms, as provided in Example 11, no common structural attributes identify the members of the genus. The current claims encompass a large genus of polymorphisms which encompass SNPs in SEQ ID NO: 19350. This large genus is represented in the specification by only the particularly

named polymorphism for which data is provided. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SNPs of SEQ ID NO: 19350 alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of SEQ ID NO: 19350 relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms. The polymorphisms shown are not representative of the genus of any polymorphism. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

***Claim Rejections - 35 USC § 112- Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1634

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 21-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-6, 21-22 are drawn to a method for identifying an individual who has an altered risk for developing stenosis by detecting a SNP in SEQ ID NO: 19350 in said individual's nucleic acids wherein the presence of the SNP is correlated with altered risk for stenosis.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art



The art teaches polymorphisms in Apolipoproteins which are not associated with severe aortic valve stenosis. APOA, AK38, plasminogen gene are all synonyms of LPA which the instant polymorphisms lies within. Avakian et al. (Clinical Genetics, Vol. 60, pages 381-384, 2001) teaches a G/A polymorphism APO A1 which is not significantly associated with AS (see Table 3). Thus, it is clear that not all polymorphisms in the gene APO A1 is associated with each stenosis.

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that

each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that any polymorphisms within SE QID NO: 19,350 is associated with any risk for any stenosis in any individual.

The specification does not provide guidance for detecting a SEQ ID NO: 19,350 SNP in any individual. Individual encompasses any human, dog, cat, mouse, ferret, gorilla, for example. The specification and the art do not provide any guidance that the polymorphic SNP is present in other animals or individuals. The specification appears to be directed to persons, i.e. humans. It is unpredictable other animals will have SEQ ID NO: 19,350, the SNP and that the SNP is associated with stenosis. Without further undue and unpredictable experimentation to determine whether the association is present over a range of individuals, a method for associating the SNP with a disease in any individual in unpredictable and undue.

The specification does not provide guidance for detecting any SNP in SEQ ID NO: 19,350. The specification teaches a single SNP location in SEQ ID NO: 19350 at position 101. It is unpredictable that there are any other SNPs in 19,350 and the location of the SNPs if there are SNPs. Further the skilled artisan would be required to

perform detailed analysis on each other position of SEQ ID NO: 19, 350 to determine if there is a polymorphism at the location and whether the polymorphism is associated with stenosis. This experimentation is unpredictable and would require undue trial and error experimentation. As shown by the prior art, SNPs located in a single gene do not predictably correlate with the same disease (see CADPKL for example).

The specification does not provide guidance for any altered risk for the SNP at position 101 of 19,350. The specification teaches hCV2590271, SEQ ID NO: 19,350 was analyzed in S0012 and V0002 samples. As seen in Table 7, page 5, the hCV25930271 is not significantly associated with coronary stenosis in the second population (p-value 0.41193). It is thus unpredictable whether the SNP is predictably associated with stenosis given the unpredictable association in two different stenosis populations. The specification teaches there is an association between the SNP and coronary stenosis in population 1. However, it is unpredictable given the varying statistical data provided in the specification whether the skilled artisan could make and use the instant invention without further unpredictable and undue experimentation.

Finally the specification does not provide any guidance for an association of position 101 of SEQ ID NO: 19350 with any stenosis. Stenosis broadly encompasses coronary stenosis, spinal stenosis, aortic stenosis, lumbar spinal stenosis, aortic valve stenosis, mitral valve stenosis, pulmonary valve stenosis, tricuspid valve stenosis, pyloric stenosis. The specification teaches analyzing two populations with varying degrees of coronary artery stenosis. It is unpredictable that each of these diseases is associated with the same SNP to a significant level. Each of these diseases is distinct and do not share the same mode of operation. Moreover, as seen above, the prior art teaches mutations in APOA1 are not associated with a particular stenosis.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

#### Level of Skill in the Art

The level of skill in the art is deemed to be high.

#### Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, it is unpredictable any polymorphisms is associated with altered risk any stenosis in any individual. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it

Art Unit: 1634

is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Conclusion***

**8. No claims allowable.**

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.



**Jeanine Goldberg**

**Primary Examiner**

June 19, 2006